THE WALTER AND ELIZA HALL INSTITUTE OF RESEARCH IN PATHOLOGY AND MEDICINE

THE DIRECTOR'S NINETEENTH ANNUAL REPORT

1937-38

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Historical Preface

The Walter and Eliza Hall Institute of Research in Pathology and Medicine was founded in 1916. The Trustees of the late Walter and Eliza Hall completed the Pathological Block of the present Royal Melbourne Hospital, and provided an annual payment of £2,500 towards the upkeep of the Institute. In 1925 this was increased to £3,100, and since 1930 has been £3,200 annually. In addition, the Institute has received, since its inception, £500 per annum from the University, the Medical Staff of the Melbourne Hospital having agreed that this portion of its clinical fund should be so used. Since 1925 a further sum of £250 per annum has been provided by the University from interest on the Appeal Fund (1924), together with an annual contribution from the Clinical Research Fund.

In 1926 the late Sir Aaron Danks, then President of the Melbourne Hospital, established an Endowment Fund to support a Biochemical Department. This fund has now reached the total of £8,591. The Edward Wilson Trustees maintained this new department by contributing £1,500 per annum in 1926, 1927 and 1928, and £1,000 in 1929. This Trust also, in 1926, contributed £3,000 for the foundation of an Institute Library, and of this sum £2,000 has been invested as endowment.

The Institute has been supported by annual contributions from the Felton Bequest Committee (since 1928), the Trustees of the late Anthony Mackie (since 1933), and the Trustees of the late T. J. Sumner (since 1929).

The Institute has also received substantial support from the Department of Health of the Commonwealth Government; in the years 1927, 1928, 1929, 1930 and 1931 a total of £10,650 was received for special researches. In 1934 the Commonwealth Government entered into an agreement with the Rockefeller Foundation that each would contribute to the Institute the sum of £1,000 per annum for the ensuing three years to support work on Virus diseases, particularly those affecting the central nervous system. The Rockefeller Foundation and the Department of Health of the Government agreed in 1937 to continue their support of the work on Virus diseases for a further two years, and the National Health and Medical Research Council contributed a further sum of £750 for the general expenses of this department for the year 1938.

In 1932, by the will of the late Mrs. L. E. W. Carty, of Brisbane Hill, Hamilton, the Elsie Marion Carty Fund was founded. Mrs. Carty willed to the Institute a portion of her estate and a residuary interest therein to establish this Fund. It was her wish that the income should be used, primarily, for the assistance of promising research workers.

From 1934 to 1937 Mr. A. M. Nicholas gave an annual sum of £250 towards the salary of the Assistant Director, and Mrs. Nicholas has generously continued this contribution.

In 1936 the Carnegie Corporation of New York paid the travelling expenses of Dr. Feldberg, and have contributed in addition 4,500 dollars which, with £1,100 collected by Mr. Reuben Hallenstein, made it possible to bring out this worker and maintain him up to the present time.

Last year the establishment of the National Health and Medical Research Council opened a new era in medical research in Australia, and in the present year much of the research in this Institute is being assisted by grants from this source.

The Institute is controlled by a Board consisting of representatives of the Walter and Eliza Hall Trust, of the University of Melbourne, and of the Committee of Management and Medical Staff of the Royal Melbourne Hospital. During the war years Professor Sir Harry Allen acted as Honorary Director. In 1919 Dr. S. W. Patterson was appointed first Director; in April, 1923, he resigned, and was succeeded by Dr. C. H. Kellaway in August, 1923. During the interval Mr. H. Dew acted as Director.

The Director's Nineteenth Annual Report

TO THE BOARD

OF THE

Walter and Eliza Hall Institute of Research in Pathology and Medicine

JULY, 1938.

The outstanding event of the year under review was the establishment by the Commonwealth Government of the National Health and Medical Research Council. This has been of great assistance to the Institute. Dr. Wilhelm Feldberg is to be appointed a Senior Research Fellow, and additional salary has been provided for Dr. Burnet in consideration of his acting in an advisory capacity and training workers in his field. Dr. E. R. Trethewie has been appointed a Junior Research Fellow and is working in the Department of Physiology, and Dr. A. V. Jackson is doing research on poliomyelitis with Dr. Burnet. Other assistance is mentioned in the report of the activities of the various departments.

The work in the Virus Department has included studies of influenza, Queensland Rickettsial fever, poliomyelitis, and of several viruses which specifically attack the nervous system.

The researches in the Department of Physiology have been concerned mainly with the problem of cell injury and the liberation of histamine.

In the Biochemical Department work on porphyrins and haematin has been carried out, and also studies on the relations between the proteins and heavy metals. The biochemical part of clinical researches on the effects of haemorrhage have been conducted in this department.

Clinical researches have been concerned with the effects of haemorrhage, the preparation of physiological solutions for treatment, peptic ulcer, new methods of estimation of the number of red cells and of haemoglobin and with epilepsy as a symptom of organic disease of the brain.

DEPARTMENT OF VIRUS RESEARCH.

As in previous years a large proportion of the work in this department has been concerned with the quantitative study of virus problems by the egg membrane technique. During the year several viruses not previously studied, viz., herpes, "B," and pseudo-rabies viruses, have been cultivated on the egg, and the classical strain "W.S." of influenza virus has also been adapted to produce satisfactory lesions. Dr. Burnet has contributed a section dealing with the technique of virus cultivation on the chorioallantois to the "Handbuch der Virusforschung" edited by Professor R. Doerr.

Influenza Virus.

In the course of work with influenza virus referred to in the last Annual Report, it became evident that there were definite (immunological) differences between strains of different origin. In order to study these in detail two further strains, in addition to our Melbourne strain, were adapted to egg titration by continued passage. The strain "W.S.," with which most of the English work on influenza has been carried out, soon developed a satisfactory activity. After 50 passages it is now even more highly pathogenic for the egg than the egg-adapted Melbourne virus. It is still, however, highly pathogenic for mice, and produces a typical fever in the ferret. Shope's Swine influenza strain has proved much more difficult to adapt. There is no difficulty in propagating it from egg to egg, but the lesions remain small, and no lethal action on the embryo develops. It was found possible to use the strain for egg membrane titrations of the corresponding antibody, but the counts obtained were not so regular as was the case with the two human strains.

Study of the antibody content of human and experimental sera, using these three strains in both egg-adapted and mouse-adapted forms, has given some results of interest.

In the first place it has been shown that the strains "W.S.," "Melbourne," and "Swine" are antigenically almost totally distinct if tests are made with sera from immune ferrets. All the human strains which are available to us can be placed in one of two groups. The first includes "Melbourne" and the two American strains, "Philadelphia" and "P.R.8"; the second contains two English strains, "W.S.," "B.H.," and two strains from Leningrad and Moscow respectively. Minor antigenic differences within the groups appear to exist, but the primary differentiation is clear-cut.

The reactions of human sera with different strains of influenza virus are complicated, particularly when adult sera are used. Sera of children in Melbourne, however, show relatively specific antibody. If antibody is present at all, it is active only against the strain "Melbourne," not against "W.S." and "Swine." Adult sera show varying degrees of activity, but in general they possess a high activity against "Swine," while their action on the two human types may vary over a wide range, but is as a rule approximately equal for each. The change in type from the childhood to the adult pattern appears to take place gradually between the ages of ten and sixteen.

Infants at birth possess sera with the immunological properties of the adult, but all antibodies are rapidly lost, and from six months to one year the serum has no power of inactivating any type of influenza virus. A large series of children's sera, taken about two years after the last prevalence of influenza in Melbourne, showed none under that age to possess antibody. A proportion of older children from three upward possessed relatively large amounts of specific antibody against "Melbourne."

Absorption experiments show that all types of antibody can be removed from adult serum by "Swine" virus. This is regarded as almost conclusive evidence that the activity against "Swine" is a manifestation of generalised antibody, not a relic of infection in 1918-19 by a virus with "Swine" type antigenic structure.

The complement fixation reaction in influenza has been used by Miss Lush in conjunction with the virus-neutralisation tests. It shows a much lower degree of specificity than the latter. Egg membrane lesions have provided satisfactory antigens of each type of influenza virus. The most interesting phase of this work was the demonstration of a systematic difference between children's sera and immune ferret sera on the one hand, and adult human sera on the other. The former (type specific) sera showed maximal fixation with the highest antigen concentrations, while adult sera (with "generalised" antibody) showed a zone phenomenon fixing complement best with more dilute antigen.

Immunisation with Egg-adapted Virus.

During the early winter of 1937 an experiment was undertaken to determine whether immunisation of human beings with living egg-adapted "Melbourne" virus provided any protection against influenza. About 200 individuals in various institutions were given two inoculations of virus intranasally by means of

an atomiser. An equal number of "controls" were arranged for in the same institutions. Thirty individuals were tested for antibody before and after such treatment.

Since no influenza epidemic occurred, little information of value was obtained. The experiment afforded confirmation of the harmlessness of the procedure. The antibody response was slight or absent in most individuals, but in two there was an increase to more than ten times their original titre. The subsequent recognition that there are at least two antigenic types of virus has reduced the likelihood that such a method of immunisation would be effective. Although we have a well adapted strain of "W.S.," this has still retained its pathogenicity for mice and ferrets, and presumably also for human beings. No further experiments on these lines are at present contemplated, unless a suitable strain of "W.S." type can also be obtained.

A detailed study is in progress of the pathology of the infections in mice, produced both by the non-pathogenic strain "Melbourne egg" and the highly pathogenic "W.S. egg," using the egg membrane technique for titration both of virus and of antibody. In the course of this work the effectiveness of immunisation with the avirulent strain against very large doses of virulent virus has been repeatedly confirmed.

Q. Fever.

Miss Freeman and Dr. Burnet have continued the study of the rickettsial organism responsible for this disease, working in close collaboration with Dr. E. H. Derrick. In the last report certain reservations were made in claiming that this organism was the cause of the Queensland disease. Since then it has been possible (1) to isolate the organism by inoculation of human blood from a typical case directly into mice, (2) to show that rickettsial emulsions are regularly agglutinated by convalescent sera from Q. fever patients and not by sera of normal individuals, and (3) to show that this agglutination first appears about ten days after the onset of fever, shows a rise in titre during the next week, and then stays relatively constant. These observations appear to provide final proof of the etiological significance of the rickettsia.

The use of emulsions of rickettsiae for agglutination tests has proved of great value in connection with epidemiological work on the disease as it occurs in Queensland. These emulsions are prepared by fractional centrifugation of emulsions from heavily infected mouse spleens and livers. It has been found that by heating the partially purified suspensions for thirty

minutes at 50° C., most of the tissue debris flocculates, leaving a suspension composed almost wholly of rickettsiae. Such suspensions are stable, and keep their specific agglutinability apparently indefinitely. The antigen concerned is heat stable, the suspensions being still agglutinable after heing heated to 100° C.

Through the co-operation of workers on rickettsiae in several parts of the world, we have obtained sera from patients or experimential animals after infection with typhus fever, scrub typhus, Rocky Mountain spotted fever, South African typhus, and tick-bite fever amongst human rickettsial infections, and sera from sheep with South African heartwater and Scottish tick-borne fever. None of these sera agglutinated the rickettsiae of Q. fever. Dr. A. Pijper, of Pretoria, very kindly tested sera from cases of each of the South African rickettsial diseases against suspensions of the Q. rickettsia sent from Melbourne. These suspensions remained agglutinable by Q. fever sera sent with them, but were unaffected by any of the South African sera. These negative results, together with the fact that Q. fever immune sera show no agglutination of Proteus strains, indicate that the micro-organism is distinct from any previously described.

Experimental infections in mice show some unusual features. They are never fatal in normal mice, and produce no obvious symptoms. The time of appearance of the maximal number of rickettsiae in spleen smears is inversely related to the dose administered. A large dose shows maximal infection in seven days. A week later very few rickettsiae are present in smears, and subinoculation to other mice is without result. Very small inocula, on the other hand, may show positive spleen smears only after three or four weeks. There is considerable variability in the intensity of infection amongst mice inoculated with the same dose, and at times it has been difficult to obtain organs sufficiently heavily infected to prepare agglutinating emulsions. Experiments at present in progress with X-irradiated mice have given more regular results, and it is hoped to overcome this difficulty by such treatment.

During the year four laboratory infections with Q. fever have occurred, two mild clinical attacks, and two sub-clinical infections. These were only recognised retrospectively by means of the agglutination test, but as in each case previous samples of sera were available and showed no agglutination, the fact of infection is fully substantiated. It is probable that transmission occurred by some arthropod vector, and a mite is under suspicion.

One of these laboratory infections could be shown to have taken place in March by the change in serum reactions—regular bleedings from this subject were being made in connection with other work—but no symptoms whatever could be recalled as occurring at this time. In November this subject experienced a short, fairly severe febrile attack of the clinical character of Q. fever, for which no other cause could be ascribed. This suggested the possibility that Q. fever, like Brill's disease in America, may remain latent for relatively long periods. The idea is supported by the observation of a case of Q. fever (proved by isolation of the rickettsia) which occurred in Melbourne in a Queensland abattoir worker who had left the abattoirs five weeks before his illness.

Dr. Burnet has cultivated the rickettsia in tissue culture, using minced chick embryo tissues in Tyrode solution. During the first six days growth is slight and only a small proportion of cells become infected, but in some of these typical cytoplasmic microcolonies have been seen. During the second week of incubation much more extensive growth occurs, and smears taken at fourteen days often show enormous numbers of rickettsiae, mostly extracellular. This behaviour is similar to that reported for other rickettsiae, and appears to indicate that growth occurs in dead, or at least severely damaged, cells rather than in living ones. The organism has now been maintained in tissue culture for more than four months without loss of virulence for mice and guinea pigs. Various chick tissues have been tested, but only pooled viscera have given good results. Liver, brain, heart, skeletal tissues, and alimentary canal separately have shown very little or no multiplication.

Miss Freeman has carried out agglutination tests on large numbers of human and animal sera sent from Queensland by Dr. Derrick. The disease has been found to occur amongst farmers in certain Queensland districts as well as in abattoir workers, and a search is being made for a mammalian reservoir in these districts. Four positive agglutinations with bandicoot sera have been obtained, but the significance of these will have to be decided by field workers in Queensland.

Poliomyelitis.

The severe epidemic of poliomyelitis in Victoria, June, 1937-February, 1938, caused much public concern, and a certain amount of investigational work has been carried out by members of the Institute staff. Dr. Burnet served as one of the members of the Consultative Council appointed by the Government to advise on the epidemic.

No difficulty was experienced in transferring the virus to monkeys, and four strains are available for future work. The symptoms produced in monkeys were variable, some being very severely paralysed, others showing fairly severe general symptoms but little paralysis. Monkeys which had recovered from the local virus were tested for immunity with the regularly fatal M.V. strain. They were all only partially immune, showing fever and tremor, with sometimes an increase in paralysis, but surviving what would have been a certainly fatal infection in a normal monkey.

In looking for evidence as to the path of entry of the virus in children, Dr. Graeme Robertson has examined histologically the olfactory bulbs of twelve patients who died of the disease. In only two of these could changes suggestive of recent infection be seen.

Dr. S. W. Williams has collected a large series of serum samples (a) from cases of poliomyelitis early in the febrile period and at a subsequent date, (b) from contact children at the time of contact, and 4-8 weeks later. These samples have been ampouled and stored for subsequent investigation.

Louping Ill.

In order to test the practicability of using egg membrane titrations for following the spread and multiplication of virus in an infected animal, Dr. Burnet and Miss Lush have studied the course of louping ill infection in the mouse after different methods of infection. By whatever route administered, the animal dies from infection of the central nervous system, and the chief problem presented was to determine the point of entry.

The egg membrane technique was found to have some important advantages for this type of work. In particular the fact that all readings of titrations were made in less than 48 hours made it possible to repeat or amplify titrations on the same material in a way impossible with standard mouse inoculation methods. The results may be summarised as follows: After intraperitoneal injection the virus passed via the blood to the nasal mucosa, and entered the central nervous system by way of the olfactory nerve and bulb in the great majority of cases. In a number of mice, however, it was evident that virus must have entered by some route other than the olfactory one. If any intracerebral damage was produced, as by the inoculation of sterile broth, death from intraperitoneal injection of virus was accelerated, and the primary multiplication in the central nervous system occurred in the damaged cerebral hemispheres. A significant, but only partial, protection against

intraperitoneal inoculation could be conferred by intranasal instillation of zinc sulphate solution.

After intranasal inoculation the virus appeared in the olfactory bulbs in two to three days, remained localised there for one to two days further, and then spread rapidly through the whole central nervous system. By the time symptoms were evident the whole central nervous system and even the peripheral nerves contained large amounts of virus.

Herpes, "B," and Pseudo Rabies Viruses.

Recent work indicates that these three viruses belong to a single group, showing some antigenic differences, but principally characterised by their differences in virulence and in their range of susceptible hosts. It is of interest that the same gradiant of virulence is evidenced on the chorioallantoic membrane. Most strains of herpes labialis will produce definite lesions on the membrane, but in our experience they cannot be successfully transferred for more than one or two passages. "B" virus produces moderately active lesions, very like those of ectromelia or myxomatosis viruses, and can be easily passaged from egg to egg. Pseudo rabies virus is highly pathogenic, producing large necrotic lesions on the chorioallantois almost like those of neurovaccinia. Dr. Jackson and Dr. Burnet are commencing a more detailed comparison of the behaviour of these viruses on the egg membrane.

Tissue Culture Studies.

In addition to the work on the cultivation of the rickettsia of Q. fever, already described, some other tissue culture studies are under way. Miss Lush has been able to confirm Sabin's statement that poliomyelitis virus can be cultivated in human embryo brain emulsions, but only one satisfactory experiment was obtained before the work had to be discontinued owing to lack of monkeys. Louping ill virus can be cultivated with regularity in such tissue, and some preliminary experiments show that influenza virus multiplies in human embryo lung tissue, but not in brain. It is hoped that work in this field may open up possibilities of dealing with human infections not transferrable to experimental animals.

Bacteriophage.

Miss Freeman has completed her studies on the phage-inhibiting activity of staphylococcal extracts. It was shown that the substance responsible was of polysaccharide character, and in addition to its phage-inhibiting activity showed precipitation with immune sera and produced a skin reaction in

suitable human subjects. On heating with alkali the substance lost its phage-inhibiting power, but retained its other qualities, thus appearing to be identical with the polysaccharide haptene obtained by Julianelle.

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"The Rickettsia of Q. Fever: Further Experimental Studies." "Medical Journal of Australia," 1938, I. 296.

F. M. Burnet:
"Influenza Virus on the Developing Egg. 5. Differentiation of Two Antigenic Types of Human Influenza Virus." "Australian Journal of Experimental Biology and Medical Science," 1937, 15, 369.

Dora Lush and F. M. Burnet:
"Influenza Virus on the Developing Egg. 6. Complement Fixation with Egg Membrane Antigens." "Australian Journal of Experimental Biology and Medical Science," 1937, 15, 375.

F. M. Burnet and Dora Lush:
"Influenza Virus on the Developing Egg. 7. The Antibodies of Experimental and Human Sera." "British Journal of Experimental Pathology," 1938, 19, 17.

Mavis Freeman:
"The Phage Inactivating Agent in Extracts of Staphylococcus Aureus." "Australian Journal of Experimental Biology and Medical Science," 1937, 15, 221.

E. V. Keogh:
"Ectodermal Lesions Produced by the Virus of Rous Sarcoma." "British Journal of Experimental Pathology," 1938, 19, 1.

DEPARTMENT OF PHYSIOLOGY.

Miss MacKay, of the Department of Physiology in the University of Adelaide, was a guest in this laboratory for a period of three months at the end of last year. In February Dr. E. R. Trethewie joined us as a Junior Research Fellow of the National Health and Medical Research Council. The funds provided by the Carnegie Corporation of New York and by

private subscription have now been exhausted, but additional funds for materials and assistance have been available for Dr. Feldberg and Dr. Trethewie from the National Health and Medical Research Council.

Experiments on Cell Injury: The Liberation of Histamine and the Formation of Lysocithin-like Substances by Venoms.

Dr. Feldberg and I have continued the experiments reported last year on cell injury and liberation of histamine. The conception that the cytolytic action of venoms is associated with the liberation of histamine, which plays an important part in producing some of the symptoms of snake venom poisoning, has been strengthened by further experiments with snake venoms and bee venom. The mechanism by which tissue cells become permeable to histamine by the action of venoms has been studied, and particularly their action on cell lipins causing the formation of a cytolytic substance or substances like lysocithin. Our experiments may conveniently be divided into three groups —(a) those in which the symptomatology of poisoning by venoms has been analysed and compared with the effects produced by histamine, (b) those in which the liberation of histamine from perfused organs has been studied, and (c) those concerned with the formation by the venoms of lysocithin-like substances in the tissues.

(a) Circulatory Effects—(i) Venom of the Indian Cobra.

In continuation of our work on cats described in the last report, Dr. Feldberg and I have analysed the effects of intravenous injection in dogs. The venom causes a fall of arterial blood pressure which results from peripheral vasodilatation, and is associated with fluid loss from the circulation brought about by changes in the permeability of the capillaries. There is no obstruction in the pulmonary circulation such as occurs in cats, but the hepatic veins are constricted, the liver is engorged, and the lymph flow from the thoracic duct increased. These are the symptoms of histamine shock in dogs. In addition, cobra venom, like histamine, produces engorgement and haemorrhages in the mucosa of the small intestine, the changes being most intense in the duodenum. Large doses of venom cause heart failure by impairment of conduction as manifested by heart block and abnormal ventricular rhythms. *Post mortem* there are subendocardial haemorrhages in the left ventricle.

(ii) The Venom of the Bee.

Plentiful supplies of this venom were given to us by Mr. David Bull. In analysing its effects it was necessary to differ-

entiate between the actions of histamine present in the venom and those of other constituents. The symptoms resulting from the latter are, to some extent, the outcome of cell injury which leads to liberation of histamine from the tissues. Histamine therefore plays a double role in the symptomatology of bee venom poisoning. The amount of histamine present in the venom varies. In cats, which are rather insensitive to bee venom, the circulatory effects of intravenous injections of small doses of crude venom are determined by the histamine present in the venom, but large doses of crude or purified venom cause long lasting changes which are independent of the histamine present. The arterial blood pressure falls; the pressure in the pulmonary artery rises; there is fluid loss from circulation and sometimes heart failure occurs. The lungs may be intensely congested and haemorrhagic. Similar effects have been observed in cats after poisoning with the venom of the Indian cobra. The circulatory effects of bee venom in dogs resemble those described above for cobra venom, except that the changes in the heart are less pronounced.

(b) Liberation of Histamine from Perfused Organs—Snake Venoms.

We had earlier demonstrated the liberation of histamine from perfused lungs of guinea pigs and cats, and have now shown that the venom of the Indian cobra produces the same result in the perfused lungs of dogs and monkeys and in the perfused liver of the dog. Trethewie obtained the same effects when the venom of the Australian black snake (*Pseudechis prophyriacus*) was injected into the perfused dog's liver. The amounts of histamine liberated depended upon the amounts available in the organs and upon the dose of venom injected. With large doses the organ was depleted of its histamine and the extensive damage of the cells was revealed by a large output of protein, and, in the case of the liver, by depigmentation.

Venom of the Bee.

The effect of bee venom in liberating histamine is similar to that of cobra venom. When it was injected into the perfused lungs of guinea pigs and dogs, and into the perfused liver of dogs, it caused a prolonged output of histamine and a large output of protein; in the case of the liver, depigmentation occurred. With the injection of venom equivalent to 5 to 20 stings from between 40-75 p.c. of the tissue histamine could be liberated from a perfused lobe of the lung or liver.

(c) Formation of Lysocithin-like Substances from Tissue Lipins.

When perfusate collected from perfused organs, after the injection of venom, was assayed on the guinea pig's gut it contained not only histamine, but also a substance or substances which caused a slow delayed contraction of the guinea pig's jejunum and evanescent changes in its excitability. In experiments on the monkey's liver, which contains only traces of histamine, we found that the perfusate collected after the intraportal injection of venom contained no appreciable quantity of histamine. But it contained the substance which caused slow contraction of the gut and after-changes in excitability. This substance must have been formed by the action of cobra venom on the tissues, since it was present in large quantities in extracts of envenomed liver, whereas those of normal liver had only a weak action of that kind. The substance was found to be soluble in absolute methyl-alcohol. This enabled us to concentrate it, and facilitated a study of its properties.

It is known that snake venoms act on lecithin *in vitro* by splitting off oleic acid and that the resulting rest, lysocithin has a strongly haemolytic action. It was conceivable that a similar action might occur in the tissues, and that the slow stimulating action on the gut of perfusates and extracts from envenomed liver resulted from the presence of lysocithin-like substances formed by the action of venom on tissue lipins. This assumption was verified in that we were able to show that extracts of envenomed liver were haemolytic, and that alcoholic extracts of lecithin treated with cobra venom were not only haemolytic, but had the characteristic effects on the guinea pig's jejunum. Both these extracts were shown to be free from venom. Between their haemolytic and muscle stimulating properties there were quantitative differences. Since these were only in part accounted for by the antihaemolytic property of liver extracts, they suggested the presence in our extracts of at least two active substances, one of which was lysocithin. We have therefore provisionally regarded the activity of perfusates and extracts of envenomed organs as being due to lysocithin-like substances. Their formation probably represents an intermediate step in the liberation of histamine, since we were able to show that both the extracts of envenomed monkey's liver and of lecithin treated by venom liberate histamine from perfused organs. In addition, many of the symptoms of venom poisoning which cannot be explained by liberation of histamine, and which have been attributed to the "direct" action of the venom, may result from other actions of lysocithin-like substances. This assumption has been substantiated by comparison

of the effects of cobra venom with those of extracts of envenomed liver and of lecithin treated by venom. Recently Trethewie has repeated the experiments concerning the formation of lysocithin-like substances in the perfused liver, using the venom of the Australian black snake. From experiments which Dr. Feldberg and I have carried out with bee venom it can be concluded that this venom also has a similar action on tissue lipins.

The formation of lysocithin-like substances in the tissues may not be confined to venoms, but may play a part in the action of other haemolytic poisons, and even in less extensive cell injury, such as is brought about by the antigen-antibody reaction of anaphylaxis, by peptone, or by ultraviolet light. There is at present no direct evidence for this more general hypothesis, but there are a few indications in its favour, and the formation of cleavage products from tissue lipins would remove many of the inherent difficulties of the histamine theory of cell injury.

Experiments on Histamine and Acetylcholine in the Tissues.

There has been much speculation concerning the origin of the histamine present in many organs. The assumption that it is derived from histidine was supported by recent observations of Pinosch and Bloch, who found an increase in the histamine content of the guinea pig's lungs after a subcutaneous injection of histidine. Miss MacKay has repeated their experiments, but has not been able to confirm them. The range of individual variation in the histamine content of the lung is so great as to cover the values obtained by Pinosch and Bloch in normal, as well as in injected, animals.

Trethewie has investigated the question of the existence in the tissues of "bound" and "free" histamine and acetylcholine. French authors claim that two such states exist for the latter. Their claim is based mainly on the observation that the acetylcholine content of saline extracts of organs ground with quartz powder increases when the extracts are heated. It is assumed that heating sets free the "bound" acetylcholine. Trethewie has made a similar observation for the histamine content of saline extracts of the dog's liver. Heating the extract greatly increases the histamine yield, but after thorough centrifugation the activity of the extracts, which have been thus freed from tissue cells and debris, was unaltered by heating. The increase in the activity of uncentrifuged extracts by heating must therefore be attributed to the

destruction of tissue cells with the liberation of intracellular histamine. He has confirmed the observations on acetylcholine and shown that they have a similar explanation.

On 25th November, 1937, I gave the Sir Richard Stawell Oration at Melbourne on Medical Research in Australia, and on 3rd June, 1938, the Bancroft Lecture at Brisbane on Cellular Response to Injury.

W. Feldberg and C. H. Kellaway:

"Circulatory Effects of the Venom of the Indian Cobra (Naia naia) in Dogs." "The Australian Journal of Experimental Biology and Medical Science," 1937, 15, 441.

"Liberation of Histamine from Perfused Lung of the Guinea Pig by Bee Venom." "Proceedings of the Physiological Society," 16th October, 1937; "Journal of Physiology," vol. 91.

"Liberation of Histamine and its Role in the Symptomatology of Bee Venom Poisoning." "The Australian Journal of Experimental Biology and Medical Science," 1937, 15, 461.

"Liberation of Histamine and Formation of Lysocithin-like Substances by Cobra Venom." "Journal of Physiology" (in the press).

Miss M. MacKay:

"The Effect of Histidine on the Histamine Content of the Lungs and on Histamine Reactions." "The Australian Journal of Experimental Biology and Medical Science" 1938, 16, 137.

E. R. Trethewie:

"Experiments on the Problem of 'Free' and 'Bound' Histamine and Acetylcholine." "The Australian Journal of Experimental Biology and Medical Science" (in the press).

C. H. Kellaway:

The Sir Richard Stawell Oration. "Medical Journal of Australia," 26th February, 1938.

The Bancroft Memorial Lecture for 1938—"Cellular Response to Injury" (in the press).

Studies in Nerve Regeneration.

Dr. Basil Kilvington has been continuing his studies on nerve regeneration. These have been directed mainly to demonstrating the alteration in the nerve tracks after division and suture of a peripheral nerve. Among the changes which occur are:—

1. Growth of non-functional motor fibres down old sensory paths.

2. Where motor fibres grow down to motor-end plates and lead to recovery, this does not always occur with corresponding central and peripheral fibres. This largely explains defective recovery of fine movements after nerve division.

3. After nerve division and suture, branching of the fibres often occurs where the cut has been made, so that a single fibre may innervate antagonistic muscles by bifurcation.

4. Where the central end of one nerve is joined to the peripheral ends of two or more nerves, this branching attempts to make up for the disparity in number between the central and distal fibres. At the same time this leads to lack of adjustment in the action of the muscles supplied. In one case the average number of peripheral fibres supplied by a single central one was three. In this animal though all the muscles responded to Faradism, yet the co-ordination in walking was poor in the hind limb affected.

BIOCHEMICAL DEPARTMENT.

Blood Pigments.

Mr. Holden has studied the effect of pH and of the presence of proteins on the ultraviolet absorption spectra of porphyrins and of haematin, with a view to ascertaining whether proteins, other than the globin of the blood pigment, could combine with these substances. One of the proteins of serum was found to form compounds, but other proteins tried, such as casein, could not. The work was continued on denatured globin, carefully freed from all traces of the native protein. The compound of denatured globin and haematin had the same U-V spectrum in faintly alkaline solution as that of globin and haematin (alkaline methaemoglobin). The spectrum peculiar to methaemoglobin and, presumably, indicative of that type of combination which distinguishes globin from all other known proteins only appears at pH 4.4 to 6.0. Outside this range it turns on the acid side to that of acid haematin, and on the alkaline to that of alkaline methaemoglobin. The spectrum of proto porphyrin-denatured globin appears to be peculiar to itself.

Mr. Holden and Mr. Setter investigated the effect of alcohol and of acetone on the blood pigments of various species. No great differences were found. That of the cat was most resistant to the denaturing effect of these solvents; that of the pig, the least. In the presence of certain colloids, notably gum ghatti,

the blood pigments of the common mammals could be precipitated at laboratory temperature (18-20° C.) and redissolved without being denatured. The mechanism of the effect is obscure, and it cannot at present be correlated with any allied phenomena.

Mr. Holden has carried out some research on glass electrode equipment suitable for large numbers of determinations on small samples.

Effect of Zinc Ions on Erythrocytes.

Miss Bick worked part time on the relation of zinc ions to erythrocytes, and observed that they could be agglutinated by small quantities of zinc salts and that the zinc salts could subsequently be removed by washing. The agglutinated cells could be readily haemolysed by saponin or black snake venom. The cells gave off oxygen or took it up as readily as normal cells. The amount of zinc required was less than that required to precipitate the oxyhaemoglobin present. From October, 1937, to January, 1938, Miss Bick took over the routine electrocardiography of the Royal Melbourne Hospital, and this research was necessarily interrupted.

In January the National Health and Medical Research Council, having made funds available, we were able to secure the services of Mr. Rawlinson for further investigation of the relations between proteins and heavy metals. He has worked on compounds of zinc and oxyhaemoglobin, and finds that over a limited range of pH a compound appears to exist which is insoluble in water, but which combines with oxygen reversibly just like normal haemoglobin. The compound is soluble in acid or alkali, and is reprecipitated on neutralisation. It is surprisingly stable, and the zinc ions do not appear to have any denaturant effect. This interesting compound possesses at once the characters that are used to define both the native protein oxyhaemoglobin and the irrenaturable protein parahaematin.

Biochemistry for Clinical Research.

In January Miss Bick returned to this laboratory to carry out, for Dr. Ian Wood, analyses of material from patients suffering from the effects of severe haemorrhage, and to work on the problem of the storage of blood for transfusion. The first part of her work is discussed elsewhere, and reference is only necessary to the development of micro methods so that with a sample of blood of 6 c.c. analyses may be performed for the estimation of sugar, chloride, urea, calcium, and plasma proteins, and the alkali reserve and plasma cell ratio may be determined.

Storage of Blood for Transfusion.

In studying the nature of the changes in stored blood and attempting to ascertain the conditions under which it undergoes the minimum amount of change during storage, the pH of blood and the effect of changes in osmotic pressure were first investigated. The latter were studied by measuring changes in conductivity, and an apparatus was made for this purpose by Mr. C. G. Setter and Mr. Holden. This consisted of an oscillator and a simple bridge of very low inductance with a conductivity cell fitted into a non-conducting frame. The pH measurements were made with the glass electrode. It appeared that the osmotic pressure of the outside fluid had little effect on the "life" of red cells during storage, and that the stored cells haemolyse within the limits within which fresh cells are stable. Miss Bick has made determinations on stored blood of glucose, urea, creatinine, and total and non-protein nitrogen. By these analyses she has confirmed the view, which the physical experiments suggested, that deterioration of blood during storage is primarily associated with the metabolic activities of the red cells. The glucose disappears and the end-products of nitrogenous metabolism slowly increase. Miss Bick's results suggest that the chemical reactions occurring in blood during storage are of similar character to those assumed to be responsible for the nitrogenous constituents of urine other than these derived from the diet. It was found possible to delay, to some extent, the haemolysis which occurs when blood is stored by the addition to the fresh blood of small amounts of glucose.

During January and February Mr. Dean, a student of Melbourne University, worked in the laboratory in a voluntary capacity on the determination of protein in small samples (0.1 c.c.) of plasma. He obtained quantitative coagulation by heating the diluted plasma after saturating it with amyl alcohol. He also did some comparative studies on buffer solutions with the glass electrode.

During part of March and April Miss D. Anderson worked in the laboratory on protein coagulation before leaving to take up an appointment at Sydney University.

Dr. Lemberg, of the Kolling Institute of Medical Research, the Royal North Shore Hospital, Sydney, visited us at Easter, and did some work on the ultraviolet absorption spectra of some new intermediate compounds in bile pigment metabolism.

In addition to these research activities in the department, a good deal of time is spent in preparing substances, not other-

wise available, for the use of workers in other departments. For example, preparations of crystalline egg albumen, of pure lecithin, and of lysocithin have been made for use in the experiments on cell injury in the Department of Physiology.

H. F. Holden:

"The Combination with Proteins of Certain Porphyrins." "The Australian Journal of Experimental Biology and Medical Science," 1937, 15, 409.

"The Combination of Denatured Globin with Haematin and Protoporphyrin." "The Australian Journal of Experimental Biology and Medical Science," 1938, 16, 153.

"The Effect of Organic Solvents on the Blood Pigments." "The Australian Journal of Experimental Biology and Medical Science" (in the press).

"The Use of the Glass Electrode in the Biological Laboratory" (in the press).

CLINICAL RESEARCH.

Gastro-Duodenal Haemorrhage.

During the last two years Dr. Ian Wood, the Marion Carty Research Fellow, has studied certain biochemical changes in the blood, particularly those in the urea level after massive gastric haemorrhage. It was hoped that this work could be extended so that other biochemical changes could be co-related with the clinical condition of the patient before, and after, massive blood transfusion. This has been made possible by the provision of a biochemist by the National Health and Medical Research Council. Accurate records are also being made of caloric intake of the food by mouth, and the composition of the urine, faeces, and vomitus. The Dietetic Department of the Hospital, under Sister Lelean, is co-operating in this work, and Miss Carter, a student of the department, is undertaking the study from a dietetic standpoint.

During the year Dr. Ian Wood and Dr. R. J. Wright-Smith discussed the pathology and treatment of peptic ulcer at a meeting of the British Medical Association. Dr. Wright-Smith's contribution is discussed elsewhere. Dr. Ian Wood discussed the causation and treatment of haemorrhage from peptic ulcer, and made special reference to further changes which have been made in the technique of massive blood transfusion. Many of the toxic reactions in the patient have now been eliminated, and some excellent results have been obtained. The beneficial effects of the high caloric feeding soon after the

occurrence of haematemesis are being studied. This principle was first introduced by Meulengracht, and the present investigation supports his contention that the patients are far happier when given food and fluids in liberal quantities by mouth. Furthermore, haemorrhages are less likely to occur.

IAN J. WOOD:

"The Bleeding Peptic Ulcer." "Medical Journal of Australia," 11th December, 1937.

"The Indications for Blood Transfusion." "Medical Journal of Australia," 23rd April, 1938.

Gastroscopy.

In order to gain further information on gastric pathology over fifty patients have now been studied by means of the Wolf-Schindler gastroscope. This procedure may be instrumental in making an early diagnosis of carcinoma of the stomach, and it is already placing on a sound footing the much debated problem of "chronic gastritis."

Dr. Ian Wood is using it for the diagnosis and localisation of ulcers which have recently caused massive gastric haemorrhage. We are indebted to Dr. John Horan, of St. Vincent's Hospital, for much practical help in the technique of gastroscopy.

Preparation of Physiological Solutions.

Miss F. Eleanor Williams and Dr. Ian Wood have continued their investigations on the preparation of physiological fluids for intravenous injection by the continuous drip method. By careful bacterial filtration and adequate cleansing of the apparatus the toxic effects so often caused by intravenous therapy have been eliminated. In one patient, suffering from paralytic ileus, to compensate for the fluid loss by vomiting and aspiration from the stomach, thirty pints of Ringer's solution were injected intravenously. The patient made a good recovery.

Dr. Lucy Bryce, Miss Beryl Splatt, and Dr. Ian Wood have studied the effect of A. F. Hartmann's treatment by the intravenous injection of sodium lactate to counteract the acidosis of diabetic coma. Some encouraging results have been obtained.

IAN J. WOOD:

"Treatment of Ileus with Special Reference to Continuous Stomach Aspiration with Massive Intravenous Infusion." "Australian and New Zealand Journal of Surgery," July, 1938.

Ian J. Wood and Lucy M. Bryce:
"Treatment of a Case of Severe Diabetic Coma with Hartmann's Sodium Lactate Solution." "Medical Journal of Australia," 27th November, 1937.

A New Method for the Determination of Red Cell Counts.

Dr. E. E. K. Bottomley, the lecturer in Histology at the University, has been given a grant from the Marion Carty Fund to carry out an investigation of rapid methods of estimation of red cell counts and haemoglobin percentages devised by Dr. R. C. Johnson, the Master of Queen's College. These methods have so far been tested adequately only upon normal subjects. At the same time Dr. Bottomley will endeavour to ascertain the normal haemoglobin percentage, red cell count, and red cell diameter for the healthy young Australian adult. This latter work will be carried out in the Department of Anatomy at the University.

Clinical Research by the Resident Medical Staff of the Royal Melbourne Hospital.

Although the studies enumerated in this paragraph are independent of the Institute, I cannot refrain from mentioning them here. The Medical Superintendent, Dr. Bolton, has made an interesting statistical study of the vaccine treatment of pneumonia, and his results will shortly be published in the "Quarterly Journal of Medicine." Dr. Dreverman is investigating the fluctuations in the level of the blood urea in a normal individual when subjected to various changes of diet and muscular exertion, and Dr. Marshman has made records of the gastric secretions during the hours of sleep, and has shown that hyperchlorhydria often occurs.

Neurological Research.

Dr. Graeme Robertson has continued his clinical and pathological studies on the neurological material available in the Hospital, and has contributed two clinical papers on Epilepsy and on Spinal Arachnoiditis.

Epilepsy was considered as a symptom of organic lesions of the brain, and histories of patients, whose epilepsy was characteristic of disturbances of different regions, were detailed together with the lesions determined by investigation, operation, or autopsy. Cases illustrating various pathological causes, neoplasms, injuries, aneurysms, vascular lesions, inflammation, and cerebral degeneration were described. Stress was laid upon the frequency of cerebral degenerative conditions as causes of Jacksonian epilepsy. Although treatment had often

to be symptomatic, the removal of the cause was possible in some of these. Excision of cortical scars in post-traumatic cases was possible. The results of recent investigations of the epileptic processes by electro-encephalography were described.

Five cases of spinal arachnoiditis were described. One had an acute onset and symptoms suggesting a tumour of the cervical portion of the spinal cord. The operative division of a filmy adhesion resulted in complete cure. A second with cervical localisation showed a remarkable recovery of the power and bulk of the intrinsic muscles of the hands after operation. Adhesions following a neuritis of the cauda equina were postulated in another patient. The use of lipiodol was illustrated, and the minutiae which contribute towards diagnosis were discussed. Root pains are frequent, and may commence over one or more spinal segment and later become bilateral and spread over a wide cutaneous area, or over remote areas. The pain may be influenced by posture, movement, and coughing, and is frequently of burning quality. Signs of involvement of the pyramidal tracts may appear later, followed sometimes by impairment of the sensory pathways. X-ray therapy may relieve the pain, but has no influence upon the underlying pathological process. Although trauma, syphilis, and other infective diseases have been found to precede the onset, the essential cause is unknown.

E. Graeme Robertson:

"Epilepsy as a Symptom of Organic Lesions of the Brain." "The Medical Journal of Australia," 28th August, 1937.

"Spinal Arachnoiditis." "The Medical Journal of Australia" (in the press).

ROUTINE HOSPITAL SERVICES.

Bacteriology and Clinical Pathology.

During the past year tests along the same lines as formerly have been carried out in bacteriology, serology, and haematology. These comprised 7785 tests for 5357 in-patients and 8237 tests for 4982 out-patients, and included 2348 allergic tests for 112 patients, for some of which therapeutic desensitisation was carried out. Wassermann and Gonococcal complement fixation tests numbered 3392.

The work in collaboration with the Medical Superintendent on patients with pneumonia is being continued, and the type of the infecting pneumococcus determined as early as possible in each case. An estimation of the potency of a commercial liver extract prepared for intramuscular injection was undertaken.

Dr. T. E. Wilson was appointed Resident Assistant Clinical Pathologist for 1938, and began his duties on 1st February.

Biochemistry and Basal Metabolism.

Owing to the generosity of the Carnegie Corporation of New York it has been possible to send Miss Splatt to England to work at the Courtauld Institute, and to gain experience there of the latest methods in clinical biochemistry. During Miss Splatt's absence the work of this department has been carried out by Miss Verney South.

Miss Nancy Perrins, B.Sc., spent eight months in the department learning methods, and rendered valuable assistance in the routine biochemical work.

We have estimated the output of vitamin C. in urine in a number of patients, from the results of which test the activity or otherwise of their infection has been determined.

Colorimetric methods employed at the Courtauld Institute, Middlesex Hospital, London, are being introduced gradually to replace the more lengthy technique which has been used previously, and the Benedict-Roth Metabolism Apparatus has been introduced instead of the Douglas Bag for estimating basal metabolic rates.

Electrocardiography Department.

During the year 808 electrocardiograms have been taken with the "Mathews" Portable Instrument presented by the ladies of the Box Hill and Mont Albert Auxiliary in 1932. During recent months requests for lead IV have been numerous. Lead IV has been standardised, being taken from the "Apex" and the left leg.

Morbid Anatomy.

During the year 520 autopsies were performed. Dr. C. H. Mollison and Dr. Wright-Smith were responsible for the examination of biopsy sections which numbered 1079. Sections taken from autopsy material numbered 937. Routine examination of the vermiform appendix removed at operation over a period of six months was carried out on 263 occasions. The routine photography, clinical and pathological and photomicrography have been done by Miss Helen Wischusen.

The Casoni reaction for hydatid disease was carried out by Dr. Wright-Smith in 162 patients, with a positive result on 14 occasions.

Peptic Ulcer.

Dr. Wright-Smith analysed 218 fatal cases of peptic ulceration which were studied at autopsy. The great majority of these (200) were naturally chronic. In 42 gastric and 20 duodenal ulcers haemorrhage caused the death of the patient. The cases were discussed from the standpoint of the site of ulceration and its accessibility for surgical treatment. The chronic gastric ulcers were for the most part on the "gastric pathway," either at the pylorus or on the lesser curvature, midway between the pylorus and the cardia. The duodenal ulcers were in the first part on the posterior wall. The difficulties of localisation without opening the stomach or duodenum were discussed together with the fallacies attending localisation by inspection and palpation.

R. J. Wright-Smith:
"Peptic Ulcer. Analysis of Two Hundred and Eighteen Cases Studied at Autopsy." "Medical Journal of Australia," 11th December, 1937.

Museum.

New specimens added to the museum included adenoma of the breast, amoebic dysentery, oesophagus in achalasia of the cardia, traumatic rupture of the heart, typhoid ulceration of caecum, liver abscess, and sarcoma of the ulna.

Teaching.

Dr. Burnet has given two lectures on virus diseases to fourth year students as part of the course of University lectures in bacteriology.

Dr. Wright-Smith has given the usual course of tutorial lectures in pathology to fourth year students in November and December. Lectures in elementary bacteriology were given to student nurses in the Hospital, and demonstrations of pathological material were given to the honorary staff at clinical meetings through the year.

Dr. Hilda Gardner has conducted the teaching in clinical pathology for fifth year medical students.

The Library.

Our thanks for the gift of journals and books are due to the following:—L'Académie Royale de Médecine de Belgique; The Commonwealth Department of Health; The Council

of Scientific and Industrial Research; Miss Danks; Mr. Dobell, F.R.S.; Dr. Keith Fairley; The Government Institute for Infectious Diseases of the Tokyo Imperial University; The London Hospital; The Medical Research Council; The Middlesex Hospital Medical School; New York State Department of Health, Division of Laboratories and Research; Dr. R. J. Wright-Smith; La Société Royale des Sciences Médicales; The South African Institute for Medical Research; The University of Harvard, Department of Tropical Medicine; The University of Pennsylvania, Department of Pathology; The University of Tomsk.

CHARLES H. KELLAWAY,

Director.

The Walter and Eliza Hall Institute of Research in Pathology and Medicine

FINANCIAL STATEMENT FOR THE YEAR ENDED 30th JUNE, 1938.

RECEIPTS.							EXPENDITURE.						
To Balance Brought Forward from 30th June, 1937				£2,676	8	11	By Salaries and Wages	£4,125	5	2			
,, Trustees, Walter & Eliza Hall Trust	£3,200	0	0				,, Materials	350	10	5			
,, University of Melbourne	750	0	0				,, Apparatus	43	9	5			
,, Mrs. A. M. Nicholas (for 1937 and 1938)	500	0	0				,, Sundries	162	4	6			
,, Felton Bequests Committee	270	0	0				,, Repairs to Apparatus	13	19	6			
,, Estate J. Hartley	200	0	0				,, Repairs to Buildings	11	18	10			
,, Estate Alfred Edments	100	0	0				,, Publications	148	5	1			
,, Trustees, late T. J. Sumner	8	0	0				,, Bio-Chemical Dept.	455	19	11			
,, Estate Anthony Mackie	85	0	0								£5,311	12	10
,, The Danks Trust	8	11	0				,, Balance—						
,, Royal Melbourne Hospital—Refund	478	7	11				Investments	1,875	0	0			
,, Interest on Investments	121	19	6				Cash — Agent-General, London	54	9	5			
,, Fees Received and Proceeds of Materials Supplied	242	8	2				Secretary's Advance A/c.	100	0	0			
,, Refund—Virus A/c.	363	11	9				Bank of New South Wales	1,663	5	0			
				6,327	18	4					3,692	14	5
				£9,004	7	3					£9,004	7	3

THE ELSIE MARION CARTY ACCOUNT.

To Balance Brought Forward from 30th June, 1937		£123	5	9	By Salary	£150	0	0	
,, Income from Estate		348	19	8	,, Materials	3	6	8	
,, Interest on Investments		167	12	0	,, Transfer to Physiological Fund	80	15	2	
									£234 1 10
					,, Balance, Bank of New South Wales				405 15 7
		£639	17	5					£639 17 5

BIO-CHEMICAL DEPARTMENT ACCOUNT.

To Interest Transferred from Endowment Fund	£379	16	4	By Salaries and Wages	£835	16	3
,, Transfer from Income A/c.	455	19	11				
	£835	16	3		£835	16	3

LIBRARY ACCOUNT.

To Interest on Investments	£86	7	0	By Books, Journals, and Bookbinding	£78	2	4
				,, Balance, Bank of New South Wales	8	4	8
	£86	7	0		£86	7	0

VIRUS ACCOUNT.

To Commonwealth Government	£1,000	0	0				By Debit Balance Brought Forward from 30/6/37			£532 9 3
,, Rockefeller Foundation	1,000	0	0				,, Salaries and Wages			1,342 3 9
				£2,000	0	0	,, Materials			576 15 2
,, Dr. Balance, Bank of New South Wales				451	8	2				
				£2,451	8	2				£2,451 8 2

PHYSIOLOGICAL RESEARCH ACCOUNT.

To Balance Brought Forward from 30/6/37	£799	2	7	By Salaries and Wages	£761	19	10
,, Interest	23	18	9	,, Materials	61	1	6
	£823	1	4		£823	1	4

FUND FOR NEUROLOGICAL RESEARCH.

To Balance Brought Forward from 30/6/37	£500	0	0	By Salaries and Wages	£199	5	1
				,, Materials	11	2	10
				,, Preparation of Special Sera	25	0	0
				,, Balance, Bank of New South Wales	264	12	1
	£500	0	0		£500	0	0

ENDOWMENT FUNDS.

To Balance — Bio-Chemical Endowment Fund	£8,591	10	3	By Investments	£14,844	8	10
,, Elsie Marion Carty Fund	4,233	15	3	,, Bank of New South Wales	10	16	8
,, Library Fund	2,030	0	0				
	£14,855	5	6		£14,855	5	6

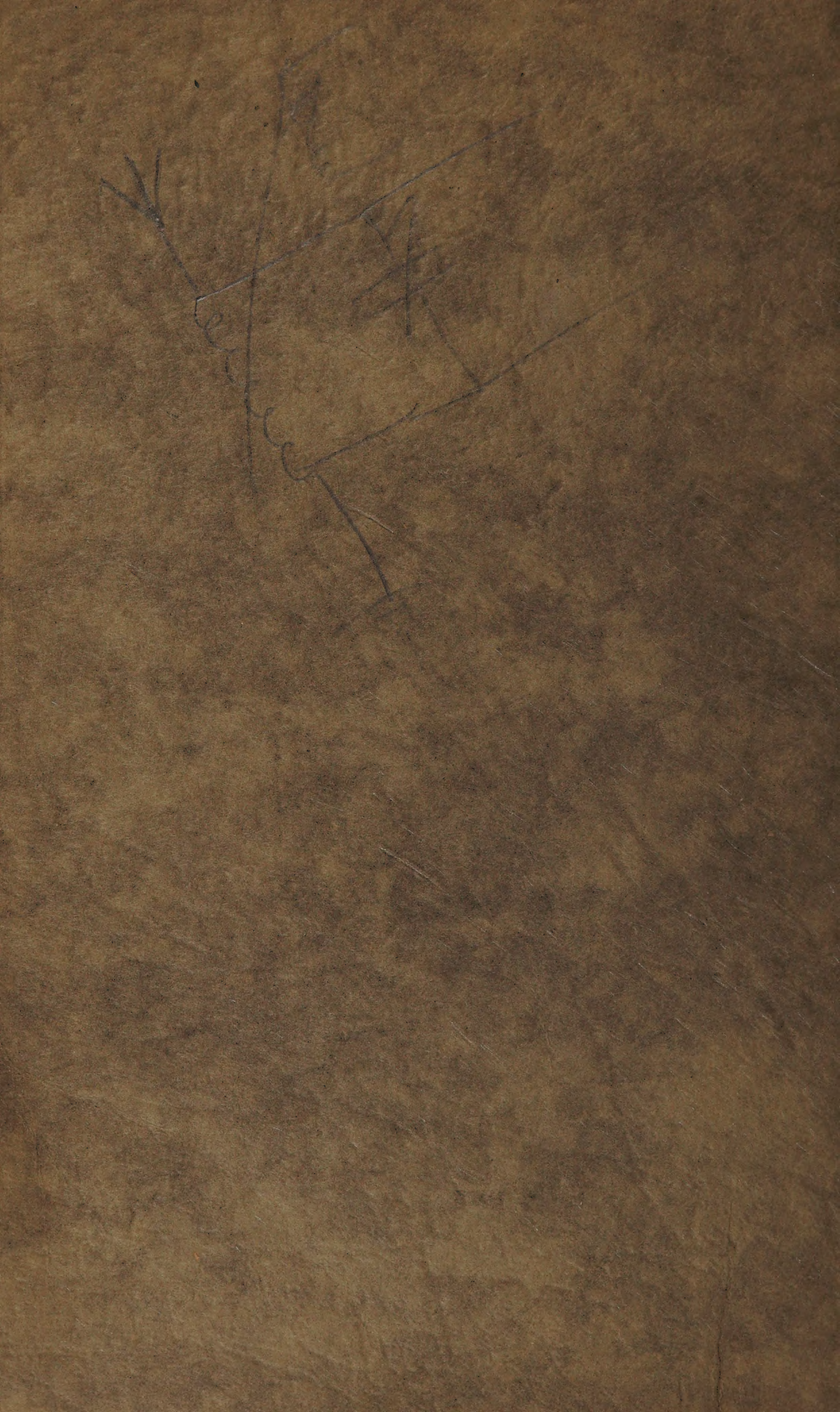
MEDICAL RESEARCH COUNCIL GRANTS.

To Commonwealth Government	£1,987	10	0	By Salaries and Wages	£696	10	0		
				„ Materials.	562	17	9		
								1,259	7 9
				„ Balance, Bank of New South Wales. .				728	2 3
	£1,987	10	0					£1,987	10 0

POLIOMYELITIS RESEARCH GRANT.

To Commonwealth Government	£1,390	17	9	By Salaries and Wages	£232	17	6		
				„ Buildings	410	14	9		
				„ Equipment	207	11	8		
				„ Materials	232	5	6		
								£1,083	9 5
				„ Balance, Bank of New South Wales				307	8 4
	£1,390	17	9					£1,390	17 9

AUDITOR'S CERTIFICATE.

I have to report that I have completed the Audit of the Books and Accounts of the Institute for the period ended 30th June, 1938. I have verified all receipts and have had vouchers produced for all disbursements. All information and explanations required have been given. The Statement is a correct statement of Receipts and Expenditure as revealed by the Books of the Institute.

14th July, 1938. W. M. JARVIE, F.C.A. (Aust.), Auditor.